EXHIBIT A

Highlights from the symposium of the Society for Medicines Research, held on December 6, 2001, in London.

Case Histories in Drug Discovery and Design 2001

by the SMR Committee

Summary

The Society for Medicines Research (SMR) held a one-day symposium, entitled "Case Histories in Drug Discovery 2001," on December 6, 2001, at the National Heart and Lung Institute in London. The talks shared one common theme: success stories in drug discovery that have led to new and improved products for therapeutic use. With an emphasis on individual contributions to drug research, each story was considered in the context of an ever-changing, high-risk industry in which research processes are complicated, the success rate is low and costs are extreme. Also incorporated in the meeting was the presentation of the "SMR Award for Drug Discovery," an award given in recognition of outstanding achievement in and contribution to drug discovery.

The Society for Medicines Research (SMR) held a one-day symposium, entitled "Case Histories in Drug Discovery 2001," on December 6, 2001, at the National Heart and Lung Institute in London. These meetings have been organized by the SMR biannually for many years, and this particular meeting, the most recent of the series, attracted more than 100 registrants. The purpose of these meetings is educational; it allows those interested in drug discovery to hear succinct accounts of recent successes. There was no overall linking theme to the talks other than the success stories in drug discovery that each described. The stories were extremely varied, but all emphasized special and individual successes that have led to new and improved products for therapeutic use. This meeting was also special for the SMR in that it presented its "SMR Award for Drug Discovery," an award given in recognition of outstanding achievement in and contribution to drug discovery. Drug discovery is a high-risk business and involves extreme costs and complicated processes, and the success rate is very low. Thus, these successes were considered in the context of the ever-changing world of the pharmaceutical industry.

Chiral drugs

The program included unrelated talks on two chiral drugs (single isomer switches), both of which have racemates currently on the market. Dr. Sverker von Unge (AstraZeneca, Sweden) described the development of *Nexium* (**esomeprazole magnesium**; Fig. 1), which is the (*S*)-enantiomer of the proton pump inhibitor *Losec* (**omeprazole**; Fig. 1), the top-selling antiulcer drug. To understand why esomeprazole was developed, it is important to know its racemate's origin and mechanism of action. Omeprazole was discovered in the late 1970s as a blocker of gastric acid secretion and was developed through a medicinal chemistry program based on a pyridine-based thioamide. Elucidation of omeprazole's mechanism of action showed that it was a prodrug that relies on a protonated form of the compound reacting with the enzyme H^+/K^+ ATPase. The basicity of the pyridine is important. While the free base is acid labile, if present in sufficient quantity, it can penetrate the parietal cells of the gastric mucosa, where-

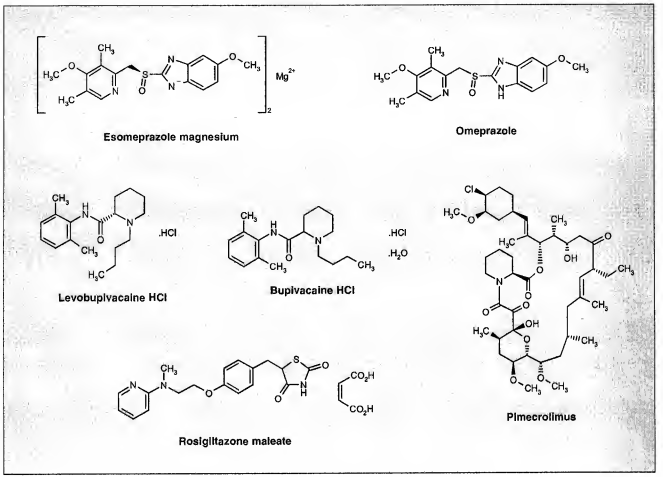

Fig. 1. Structures of selected compounds discussed at the meeting.

in the protonated form developed inside the cells accumulates because of reduced permeability. In a reversible process, a reactive intermediate is formed from the protonated omeprazole, which reacts with a mercapto group of the enzyme. Omeprazole, therefore, has a fast mode of action at the target, which leads to high selectivity and a long duration of action.

However, any successor compound of **omeprazole** would need an improved pharmacokinetic profile, less variation in the acid inhibitor effect among individuals and greater resistance to gastric juice. Several hundred compounds were synthesized in the search, but none could surpass omeprazole. An ongoing project was to fully test both enantiomers, since either might meet the requirements for a backup compound. Owing to improved methods for synthesizing large quantities of each isomer, it was shown that both isomers have identical enzyme inhibitor potency *in vitro*. However, *in vivo*, in rats, the (*R*)-isomer was more potent and had higher bioavailability compared with the (*S*)-isomer. Alkaline salts of the isomers were found to be crystalline, which was also advantageous for future clinical studies. Surprisingly, in humans, there was a reversal of isomer superiority, with the (*S*)-isomer showing 90% inhibition of stimulated acid secretion compared with 25% for the (*R*)-isomer after 15 mg p.o. at day 7. In addition, the clearance of the (*S*)-isomer was slower, being approximately one third that of the (*R*)-isomer. Individual differences were explained by variations in the metabolic enzyme CYP2C19. This form of the enzyme does not exist in the rat. In summary, **esomeprazole** is superior to omeprazole because of advantageous metabolism, greater acid control (which is faster, more sustained and more predictable) and improved clinical efficacy. The omeprazole project first began in 1972 and *Nexium* was launched in Sweden in 2000.

Dr. Robert Gristwood (Arachnova Ltd., Cambridge, U.K.) described the story behind *Chirocaine*™ (**levobupivacaine hydrochloride**; Fig. 1), the single *levo*-enantiomer of the racemic drug **bupivacaine hydrochloride** (Fig. 1), currently the leading long-acting local anesthetic. *Chirocaine* was developed through to registration by Chiroscience Ltd. (now part of the Celltech Group) and is currently mar-

keted in 11 countries (the first in 2000), including the United States. It represented the first new chemical entity from a U.K. biotech company to be approved in the United States by the U.S. FDA. This was in 1999.

Dr. Gristwood gave some background to single-isomer switches and reasons why they should be considered. Some advantages may be in their use to develop drugs that are less toxic or more potent, or that have cleaner pharmacokinetic profiles. More than 500 drugs currently exist as racemates but perhaps only 5% are suitable. Unfortunately, the properties of the enantiomers are not predictable from the racemates. For example, liver toxicity occurs with an enantiomer of **labetalol**, and QT prolongation occurs with (*R*)-**fluoxetine**.

The *Chirocaine* story provided an interesting strategic contrast to the *Nexium* story. Adopting a systematic evaluation of racemic drug opportunities, **bupivacaine** was identified as a candidate for a single-isomer switch. The decision to proceed with development in 1993 was based on Chirotscience's expertise in single-isomer synthesis and development, the hypothesis that **levobupivacaine** had similar local anesthetic activity to the racemate but lower cardiotoxicity in humans and the ability to protect the product commercially through use and process patents despite the absence of a substance-of-matter patent.

In order to evaluate data clearly, the metabolism of chiral drugs has to be considered, as it can often lead to racemization or chiral inversion, which would negate the advantages. In the case of **levobupivacaine**, the compound is metabolized to inactive species rather than to the *dextro*-isomer. Evidence from animal species showed that levobupivacaine is less toxic than the racemate (e.g. less effect in isolated hearts and less active on myocardial sodium and potassium channels). Phase I studies in humans (clinical proof-of-principle studies) researching cardiovascular parameters after intravenous administration confirmed the preclinical evidence that the *levo*-isomer was less toxic than the racemate, while in an efficacy study (ulnar nerve blockage) there was no difference in anesthetic potency. Following successful phase II studies, *Chirocaine* was licensed for a number of routes of clinical administration (e.g., epidural, intrathecal, peripheral block). Phase III efficacy studies were completed in 1996. *Chirocaine* was approved by the FDA without the black box warning regarding cardiovascular liability then associated with **bupivacaine**. It has not, however, totally displaced bupivacaine. It costs approximately 50% more than the racemate in the United Kingdom, so increased usage will depend on perceived cost benefit considerations and perceived risks with bupivacaine.

Development of pimecrolimus

Prof. Anton Stuetz (Novartis Research Institute, Vienna, Austria) described the discovery and development of **pimecrolimus** (*Elidel*, SDZ-ASM-981; Fig. 1), a new skin-selective option for topical and oral treatment of inflammatory skin diseases. Current treatments for inflammatory skin diseases such as corticosteroids, **ciclosporin** or **tacrolimus** (FK-506), have a number of deficiencies, most notably induction of skin atrophy, a lack of topical effect and systemic side effects. Pimecrolimus was the successful outcome of a structure–activity relationship study of the natural product macrolactam ascomycin. It binds in low nanomolar concentrations to macrophilin-12 and inhibits calcineurin, a phosphatase, preventing phosphorylation of a transcription factor ultimately leading to a down-regulation of inflammatory cytokines in T cells, such as interleukin-4. *Elidel* is cell-selective and highly effective in animal models of skin inflammation, such as a pig model of allergic contact dermatitis. This is predictive for humans, as the skin of the two species are very similar. Unlike corticosteroids, *Elidel* does not induce skin atrophy. With respect to tacrolimus, *Elidel* is more lipophilic with a higher affinity for skin. Thus, it distributes more preferentially in skin, but has a reduced systemic side effect profile because it permeates slowly. It is much less immunosuppressive and has an overall improved therapeutic window of antiinflammatory to immunosuppressive profile. There is minimal systemic absorption, regardless of age, and *Elidel* cream 1% shows rapid relief of atopic dermatitis and pruritus and is suitable for short-term and long-term treatment in adults, children and babies. Treatment success is maintained for six months. Orally, pimecrolimus has also been shown to be effective, safe and well-tolerated in patients with moderate to severe plaque psoriasis. By integrating disease knowledge with pharmacogenomic gene expression technology, it was possible to link mRNA expression with therapeutic progress, and also to find potential indicators of side effects by profiling blood samples following oral *Elidel* treatment. One hundred and sixty-three genes were identified with consistent behavior related to psoriasis pathophysiology, such as down-regulation of genes associated with leukocyte activation, lymphocyte infiltration and inflammatory process. No changes in gene expression were observed that might be linked to drug-related side effects. Currently *Elidel* cream is under review for registration worldwide for topical treatment and is undergoing further evaluation as an oral treatment.

Award for Drug Discovery

The 2001 SMR Award for Drug Discovery was presented to the key members of the team involved in the discovery of **rosiglitazone** (*Avandia*, BRL-49653; Fig. 1), which was developed for the treatment of type 2 diabetes. Michael Cawthorne, Steve Smith, Barrie Cantello, Richard Hindley and David Haigh, scientists from the original Beecham Pharmaceuticals program team, each received a framed certificate in recognition of their

achievement, presented by the Chairman of the SMR, Dr. David Cavalla. The monetary prize accompanying the award was donated to the charity Diabetes UK at the unanimous request of the award recipients. Dr. Steve Smith (now with GlaxoSmithKline) delivered the award lecture. The prevalence and existing treatments for diabetes provided an important background to the research effort of the team. Type 2 diabetes is a chronic disorder of glucose metabolism afflicting 5%–10% of the adult population of western societies and worldwide is predicted to rise from more than 150 million to 220 million by 2010, particularly because of statistics from China. Diabetes management requires a combination of diet, exercise and drug programs. The sulfonylureas and metformin were introduced 20–40 years ago and do not directly target the fundamental problem of insulin resistance. They do not control glucose in the long term and many patients eventually require insulin.

The research for a novel treatment for type 2 diabetes started in 1984 at Beecham Laboratories in Surrey and was based on the idea of targeting insulin resistance with small molecules. The goal was to identify compounds that would provide durable glucose control and also reduce the cardiovascular disease problems known to be associated with diabetes. At the time, virtually nothing was known about the molecular mechanisms of action of insulin, and any screen for insulin-sensitizing molecules had to rely on a catch-all mouse model of insulin resistant type 2 diabetes. Thus, the target profile for any compound of interest was defined as follows: orally potent (1 mg/kg); active in a mouse model (*ob/ob* mouse); active at three dose levels in eight-day repeat dose studies; active in dietary admixture; and assessed for efficacy by an oral glucose tolerance test with a 25% reduction in the area under the curve. The lead compound was **ciglitazone**, a thiazolidinedione derived from the hypolipidemic drug **clofibrate** and a very weak insulin sensitizer. A metabolite was found to be 30-fold more potent. Structure–activity relationship studies on the metabolite and the synthesis of more than 300 compounds led to the discovery of three potential development compounds (**BRL-48482**, **BRL-48552** and **BRL-49653**), all of which fulfilled the target profile criteria. In order to determine the final candidate choice, it was necessary to develop a selectivity screen that monitored hemodilutional effects. Any compound of interest would need to have no lowering of hematocrit in rodents at multiple doses of the antidiabetic dose. BRL-49653 was shown to be 100-fold selective and was chosen for development in 1992. The company at that time was SmithKline Beecham.

The clinical efficacy of **rosiglitazone** was established in 1995. During the early 1990s many groups had been looking to identify the molecular target of the thiazolidinediones. Thiazolidinediones were known to promote the differentiation of fat precursor cells in tissue culture for several days, which suggested a mechanism involving changes in gene expression. The peroxisome proliferator activated receptors (PPARs), ligand-activated nuclear receptors, were identified but the native ligands were unknown at the time. PPARα was shown to be a target for fibrate hypolipidemic agents and PPARγ was the target for thiazolidinedione insulin-sensitizing antidiabetic drugs. PPARγ is highly expressed in fat, but less so in skeletal muscle and liver. PPARγ activation leads to the recruitment of the retinoic acid nuclear receptor RXR, which binds to genes containing peroxisome proliferator response elements. Many of these are key genes encoding proteins that control lipid and glucose metabolism. Extensive clinical studies show that *Avandia* maintains efficacy throughout the treatment periods. This is also maintained in the presence of sulfonylureas and metformin. *Avandia* was first launched in the United States in 1999 and in the United Kingdom in 2000 and has been used in more than 2.5 million patients worldwide.

State of the industry

Successful drug discovery is a significant achievement for those involved and is a rarity, given the investment that is poured into research and development. There is a demand for an increase in new and better medicines, which puts enormous pressure on the industry to deliver. Thus, to put the stories of successful drug discovery into a wider context, SMR invited Dr. Philip Brown (Executive Chairman, PJP Publications Ltd.) to give his perspective on the state of the pharmaceutical industry and provide an assessment of its future. For an industry that has thrived since the 1950s, he asked several fundamental questions. Was the industry running out of steam? What was driving the consolidation of many companies (the mergers and acquisitions)? The biotech companies have an important part to play in supplementing large pharmaceutical companies' research activities, but given the time frame that large pharmaceutical companies are working within and the need to reinvent their product portfolios every 15 years or so in order to offset sale losses arising from patent expiration, will the biotech companies deliver on time? Overall, the rate of output of new chemical entities is no greater now than before the mergers. The generic industry is likely to be a beneficiary. With the need to charge more for medicines to recoup large investment costs and cover the shortfall in new chemical entities, this will encourage to an even greater extent the use of low-priced generics and will be a safety valve on pricing. Mergers and acquisitions promise that bigger is better, but this seems to be no more than a financial survival strategy. It is clear that the large pharmaceutical companies are the drivers, but it will be an issue to get the research and development correct. The industry has become technology-driven because of genomics. While this has provided more targets to choose from, there is a consequent

need to increase the amount of data and information in order to make the correct choices in moving forward. Transforming this into new products is taking considerable time and effort. Large pharmaceutical companies are good in the development area: marketing, distribution, dealing with regulatory authorities, etc., but the huge bureaucracies they have created may have stifled the creative research environment, preventing them from innovating at the appropriate rate. There appears to be no doubt that smaller companies with less bureaucracy, many of which are set up on the back of academic discovery, offer a creative opportunity. Something more flexible than mergers and acquisitions is needed. One solution may be for large pharmaceutical companies to create smaller cohorts from their research base to stimulate a more creative environment.

Regrettably, owing to illness and world politics, the meeting was deprived of two talks; however, the presentations given were excellent and varied examples of drug discovery and a fitting endorsement of the industry.

The SMR Committe organizes conferences on behalf of the Society for Medicines Research four times a year. These one-day conferences are of a multi-disciplinary nature, therapeutically focused and normally staged in or around London. Details about forthcoming meetings can be obtained from: SMR Secretariat, Triangle House, Broomhill Road, London, SW18 4HX, U.K. Tel: +44 (0)20 8875-2431; Fax: +44 (0)20 8875-2424; E-mail: secretariat@socmr.org; URL: http://www.socmr.org.

ABGENIX REPORTS ON FOURTH QUARTER AND YEAR-END 2001 PRODUCT DEVELOPMENT

Abgenix, Inc. reported on January 29, 2002, financial results and development highlights for the fourth quarter and year ended December 31, 2001, and laid out its expectations for 2002. In the fourth quarter of 2001, Abgenix initiated a phase II clinical trial of **ABX-EGF** as second-line monotherapy in colorectal cancer. More recently, the company, together with its co-development partner Immunex Corp., initiated two further phase II trials for ABX-EGF in prostate cancer and as first-line treatment of colorectal cancer, bringing to five the total number of phase II trials in the ABX-EGF clinical program. In May 2002, the company plans to report the results of its phase II renal cell cancer trial at the ASCO (American Society of Clinical Oncology) meeting.

Also in the fourth quarter, Abgenix filed an Investigational New Drug application (IND) for its new proprietary product **ABX-MA1**, a fully human monoclonal antibody generated from *XenoMouse*® technology for the treatment of metastatic melanoma. The filing of an IND to initiate clinical trials of **ABX-IL-8** in a wide variety of cancers was also recently announced. The first of these trials will be a phase II study in metastatic melanoma. ABX-IL-8 continues to be studied in inflammatory diseases, and the company intends to report on the phase IIb psoriasis trial in mid-2002. It hopes to complete a phase IIa trial in chronic obstructive pulmonary disease later this year. Abgenix plans to seek a co-development and commercialization collaboration partner for ABX-IL-8.

Another important development during the fourth quarter was the acquisition of rights from Gliatech Inc. to **antiproperdin antibodies**, which may have potential application in cardiovascular or inflammatory diseases. The company may choose to file an IND for one of these in 2002. Abgenix also acquired the rights to the **EGFrvIII cancer target**, a mutant form of the epidermal growth factor receptor. The target is expressed only on cancer tissue and may be a more specific target for antibody-based therapies. The company also acquired the biotechnology company Hcsed together with intellectual property and technology in the field of catalytic antibodies.

Finally, in the fourth quarter, Abgenix launched new versions of *XenoMouse* mice that produce fully human antibodies containing both lambda and kappa light chains. These new versions capture the human antibody response more completely than other transgenic mouse technologies in the commercial sector that lack the lambda light chain.

Looking forward to 2002, Abgenix plans to file INDs on two new proprietary product candidates and announce three new product IND filings by licensees. The company hopes to end 2002 with six product candidates in clinical trials in 12 indications. Enrollment will be completed this year in the phase II/III clinical trial of **ABX-CBL** in graft-versus-host disease. Other plans for 2002 include establishing antibody technology license collaborations covering up to 10 new products, and establishing additional target and technology access collaborations.